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EPIDEMIOLOGICAL MODEL FOR *CLOSTRIDIUM DIFFICILE* TRANSMISSION IN HEALTH-CARE SETTINGS

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Abstract

Objective—Recent outbreaks of *Clostridium difficile* infection (CDI) have been difficult to control, and data indicate the importance of different sources of transmission may have changed. Our objectives were to evaluate the contributions of asymptomatic and symptomatic *C. difficile* carriers to new colonizations and to determine the most important epidemiological factors influencing *C. difficile* transmission.

Design—Retrospective cohort

Setting and Patients—All patients admitted to medical wards at a large tertiary care hospital in the US from Jan 1 to Dec 31, 2008.

Methods—Data from six medical wards and published literature were used to develop a compartmental model of *C. difficile* transmission. Patients could be in one of five transition states in the model: resistant to colonization (R), susceptible to colonization (S), asymptomatically colonized without protection against CDI (C^-), asymptomatically colonized with protection against CDI (C^+), and patients with CDI (D).

Results—The contributions of C^-, C^+ and D patients to new colonizations were similar. The simulated basic reproduction number ranged from .55 to 1.99, with median 1.04. These values suggest that transmission within the ward alone from patients with CDI cannot sustain new *C. difficile* colonizations, and therefore, the admission of colonized patients plays an important role in sustaining transmission in the ward. The epidemiological parameters that ranked as the most influential were the proportion of admitted C^- and the transmission coefficient for asymptomatic carriers.

Conclusion—Our study underscores the need to further evaluate the role of asymptomatically colonized patients in *C. difficile* transmission in the healthcare setting.

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INTRODUCTION

Clostridium difficile is the leading cause of infectious diarrhea in hospitals, and has become, along with methicillin-resistant *Staphylococcus aureus*, **one of** the most common causes of health-care associated infections.[1,2] The incidence and severity of *Clostridium difficile* infection (CDI) has increased dramatically since 2000, and CDI is estimated to cause as many as 20,000 deaths and cost as much as $3.2 billion per year in US acute care facilities alone.[3–5] CDI outbreaks have become more common, and infection control-based CDI prevention efforts appear to be less effective than in the past.[2,6]

Studies on *C. difficile* nosocomial transmission were undertaken in the late eighties.[7–9] Clabots et al provided evidence that asymptomatically colonized new admissions to a ward were an important source of transmission.[9] Patients with symptomatic CDI, compared to asymptomatic *C. difficile* carriers, were more likely to contaminate their surroundings and hands of healthcare workers with *C. difficile*.[7,8] Therefore it was concluded that symptomatic CDI patients were the main source of *C. difficile* transmission. As a result, current CDI prevention efforts, such as isolation and contact precautions, target only symptomatic CDI patients[10]. Changes in the epidemiology of *C. difficile* and health care delivery since the original transmission studies were conducted may have shifted the relative contribution of symptomatic CDI patients and asymptomatic carriers.[11] For example, since 2002 alcohol-based hand hygiene products have been recommended as the primary form of hand hygiene in healthcare settings.[12] *Clostridium difficile* spores are resistant to the bactericidal effects of alcohol.[13] Use of alcohol-based hand hygiene products after caring for asymptomatic *C. difficile* carriers may increase their contribution to *C. difficile* transmission.[13] Conversely, rapid identification of patients with CDI and placing these patients in contact precautions may have reduced the contribution of *C. difficile* transmission from patients with CDI.[10,14]

Mathematical models of disease transmission provide a conceptual framework to understand and quantify transmission and intervention strategies. Mathematical models have helped to understand the epidemiology of other nosocomial pathogens such as vancomycin-resistant enterococcus[15,16] and methicillin-resistant *Staphylococcus aureus*.[17] To date, efforts to model *C. difficile* transmission have been limited; Starr et al modeled the *C. difficile* transmission in a geriatric ward.[18] They quantified *C. difficile* transmission within and between rooms, but the relative contribution of asymptomatic and clinical patients as sources of new infections was not addressed.[18] In addition, the data were collected prior to the changes in CDI epidemiology.[19]

Our objectives were to provide a framework to evaluate the relative contributions of asymptomatically and symptomatically colonized patients to new colonizations and to determine the most important epidemiological factors influencing *C. difficile* transmission at the ward level. For that purpose, we developed an epidemiological model of *C. difficile* and evaluated the impact of different epidemiological parameters on *C. difficile* transmission. We used recent data from a large tertiary care hospital and published literature to estimate model parameters.

METHODS

Data

Data were collected retrospectively from six medicine wards at Barnes-Jewish Hospital in St. Louis, Missouri from January 1 through December 31, 2008. The data were collected electronically from the hospital's medical informatics databases, and included patient demographics, dates of hospital and ward admission, discharge, and transfers, laboratory

tests, and medication exposures. Two wards had 26 beds, one ward had 29 beds, and three wards had 30 beds. On average there were 153 admissions per ward per month, including, 109 per month whose length of stay was greater than 48 hours. The microbiology laboratory at Barnes Jewish Hospital only tests diarrheal stool for the presence of *C. difficile* toxin (Remel ProSpecT *Clostridium difficile* Toxin A/B). Testing stool for the presence of *C. difficile* toxin requires a physician order. During the study period patients diagnosed with CDI were placed into isolation and contact precautions were initiated. Isolation and precautions were typically initiated only after the patient was diagnosed with CDI. The dataset included 11046 admissions. The mean age of patients was 57 years old. They have a mean Charlson Comorbidity Score of 1.8 and 54 % were female. On average there were 2.2 incident cases of clinical CDI per month on each ward (157 cases total for all six wards) and 2.2 prevalent cases (present on admission) of clinical CDI per month on each ward.

Epidemiological Model

We developed an epidemiological model for the *C. difficile* transmission in the ward (Figure 1). In an epidemiological model, the patient population is divided in different transition states according their infection status. The *C. difficile* epidemiological model included the following transition states: resistant to colonization (R), susceptible to colonization (S), asymptomatically colonized without protection against CDI (C^-), asymptomatically colonized with protection against CDI (C^+) and diseased (D, i.e. CDI) (Table 1). Resistant individuals were defined as patients who had not received antimicrobial treatment and had a normal intestinal microbiota that provides "colonization resistance" against *C. difficile*.[20] Although patients with normal flora can be colonized with *C. difficile*, this appears to be transient and associated with a much lower risk of development of CDI compared to patients with altered flora.[8,9,21] Hence, we assumed that individuals with a normal intestinal microbiota were resistant to *C. difficile* colonization. Susceptible patients received antimicrobial treatment and could be colonized by *C. difficile*. Antibiotic treatment disrupts the normal microbiota making patients significantly more susceptible to *C. difficile* colonization and development of CDI after colonization.[22] Three types of colonized patients were included in the model: C^-, C^+, and D. We considered two types of asymptomatically colonized patients based on the risk of developing CDI. Colonized patients could or could not mount a protective response. Asymptomatically colonized patients who did not mount an immune response could develop disease. Diseased patients were treated with antibiotics. Depending on treatment success, diseased patients could continue to be diseased or become susceptible again at the end of therapy. Patients could be admitted and discharged in any of the five states, and C^+ were assumed to be colonized during all the duration of the hospitalization.[7–9] The mathematical model is presented in the Appendix.

Parameterization

Model parameters are described in Table 2. The proportions of admitted patients defined as resistant and diseased were obtained from the hospital data. Patients who did not receive antibiotics during their admission were considered resistant patients. Patients with a positive stool sample within 48 hours after admissions were considered to be admitted diseased.[23] The antibiotic prescription rate was obtained from the hospital dataset based on the admission rate and the percentage of individuals that received antibiotic during their stay. Patients were considered susceptible after being exposed to antibiotics. Microflora returns to normal within 1 to 49 days after the end of the treatment depending on the antimicrobial group.[22] We set the restoration rate to 0.033 day^{-1}, which means that the microflora of each patient recovers 3.3 % each day and therefore it returns to normal after 30 days in average. Vancomycin and metronidazole are considered the "standard" treatments for CDI cases. For 80% of patients with CDI, diarrhea symptoms resolve within a typical 10-day treatment, regardless of antibiotic type.[24] Therefore the treatment rate was set to 0.10 day^{-1}, **the**

inverse of the treatment duration, and the probability of successful treatment to 0.80. The clinical disease rate is the inverse of the incubation period.[9,25] The mean fraction of colonized patients that mounted an immune response was set at 0.60; 60 % of the patients that became colonized had detectable antibody responses.[26] Discharge rates were obtained from the hospital dataset. Discharge rates are the inverse of the length of stay. Patients without antimicrobial treatment (R) during the hospitalization had the shortest length of stay (3 days). Susceptible and colonized patients had an average length of stay of 6.7 days. For clinical CDI, the length of stay was 14.7 days (Table 2). Default values for transmission coefficients and the proportion of admitted patients as S, C^-, and C^+ were set to match observed attack rates.

Simulations

The model predicted the following outcomes: the basic reproduction number (R_0), the average number of secondary cases of colonization generated by each type of admitted colonized patients (C^-, C^+, D), and the number of CDI cases per 1000 admissions. The basic reproduction number is the average number of secondary cases of colonization generated by one primary case of *C. difficile* colonization in a *C. difficile*-free ward. It conveys information regarding the transmissibility of the pathogen in a specific setting. The higher the R_0, the greater the pathogen transmissibility is. To quantify R_0 and the contribution of the three types of admitted colonized patients to new colonizations, we constructed the so-called next generation matrix for the model.[27] The next generation matrix allows us to express both outcomes as a function of the epidemiological model parameters.[27] Then, we performed a sensitivity analysis to assess which epidemiological parameters were the most influential. The method used in the sensitivity analysis was the Sobol's sensitivity indices.[28] Sobol's indices are an ANOVA-like decomposition and partition the variability of the model output (i.e, expected secondary colonizations and R_0) in main effects of the parameters and total effects (including interactions between parameters). In addition, model simulations of the stochastic model (see appendix A.2 for details) were performed to evaluate the effect of varying the proportion of admitted colonized and diseased patients and other parameters on the number of CDI cases per 1000 admissions.

RESULTS

Model simulations are presented in Figures 2, 3, 4, and 5

The R_0 ranged from 0.55 to 1.99 (Figure 2). For almost 50 % of the simulations, R_0 was less than one. One is a threshold value because if R_0 is greater than one, on average one case leads to more than one secondary case, and therefore, the number of cases will grow in the population. The variation in R_0 was explained the most by the variation in transmission parameters (β_c and β_d) and duration of the stay of the colonized patients (k *and* k_d) (Figure 2). Specifically, the two most influential parameters were the transmission coefficient for asymptomatic patients (β_c) and the discharge rate for susceptible and colonized patients (k). The proportion of the R_0 variation that was not explained directly by the parameters was a very small percentage (1 %) and was due to interactions among parameters (Figure 2).

Figure 3 displays the average number of new colonizations that each type of colonized patient can produce once admitted in a *C. difficile* free ward. These values may not be attainable because the wards are not completely occupied by susceptible individuals and have a continuous inflow of new admissions and outflow of discharges. Nevertheless, they provide a way to rank the contribution of different types of admitted colonized individuals to new colonizations. The three types of colonized patients contributed similarly to new colonizations, each resulting in an average of 0.40 new C^- colonizations and 0.60 new C^+ colonizations (Figure 3). Admitted C^- patients contribute to new cases as C^- and D (if they

move into the *D* state). The parameters that explain most of the variation in the contribution of the three types of colonized patients were the fraction of newly colonized patients that mount an immune response (*f*), the transmission coefficient for diseased patients (β_d), the transmission coefficient for asymptomatic carriers (β_c), and the discharge rate of colonized and susceptible patients (*k*).

Figures 4 and 5 display the results of the stochastic simulations. The proportion of patients admitted as C^- was the epidemiological parameter with the strongest influence on the number of new CDI cases (per 1000 admissions). For the scenario with the baseline parameters, the median for the number of CDI cases was 17.85 per 1000 admissions (Figure 4). Increasing the proportion of admitted C^- by 0.01 increases the median attack rate to 27.54 new cases per 1000 admissions. Changing the admission for C^+ and *D* had similar effects, but their influence on the number of CDI cases was lower than C^- (Figure 4). Among all the other parameter evaluated, transmission coefficients, clinical disease rate and the fraction of newly colonized patients that mount an immune response were the most influential (Figure 5).

DISCUSSION

We present a mathematical model of the transmission of C. *difficile* in health-care settings. We considered three types of colonization during hospitalization (Table 1). We omitted other states and transitions that may be relevant at the community level. Proposed models for community-associated *C. difficile* included states such as clinically resolved colonized (successfully treated CDI but patient remains colonized) and transitions such as decolonization.[29] At the hospital level, the likelihood of observing some of these states and transitions is lower because of the short duration of patient stay. For example, we assumed that the colonization lasted for the complete duration of the hospitalization because follow-up studies have indicated that patients remained colonized 30 days after discharge.[26]

The increases in CDI incidence and severity and difficulties in controlling CDI have led to the conclusion that the epidemiology of *C. difficile* has changed in recent years.[11,30] Potential explanations include alterations in healthcare practices over the last 20 years, increased asymptomatic carriage, increased patient susceptibility, and organism specific factors that have increased virulence or transmission[31]. All these changes may have increased transmission coefficients (e.g. the use of alcohol based hand hygiene products over hand washing may have increased β_c), increased the proportion of admitted asymptomatic carriers (a_{cn}, a_{cp}) and diseased patients (a_d) or decreased the fraction of colonized patients capable of mounting an immune response (*f*), among other factors. We evaluated the effect of modifying these epidemiological parameters in *C. difficile* epidemiology. The admission of colonized patients, especially C^- patients, highly influenced *C. difficile* outcomes. The number of CDI cases increased as the percentage of admitted colonized patients increased (Figure 3). In addition, the basic reproduction number ranged from 0.55 to 1.99. These values suggest that for a wide range of parameter values, transmission within the ward alone cannot sustain *C. difficile* colonization. Therefore, the admission of colonized patients plays an important role in sustaining transmission in the ward. An increase in the proportion of admitted patients who are already colonized may take place as data indicate *C. difficile* contamination of foodstuffs is more common than previously recognized and community-associated CDI is increasing.[32,33]

The number of CDI cases was also sensitive to variations in the incubation period. As the incubation period increased, the number of cases due to transmission decreased because the chances that an asymptomatic colonized patient leaves before becoming diseased increases. Therefore, increased incubation periods may increase the number of patients with

community- onset, healthcare-facility associated CDI. These patients may be readmitted later as diseased patients. Previous research indicates patients with health-care onset CDI were more likely to receive a fourth-generation cephalosporin or intravenous vancomycin that were patients with community-onset healthcare facility associated CDI.[34] These antibiotics may shorten the incubation period because of their broad impact on the normal microflora, or may be markers for sicker patients more susceptible to *C. difficile*.[22,35] Other influential parameters were the transmission coefficients and the fraction of patients that mount an immune response against *C. difficile*. These results are supported by studies demonstrating efforts to reduce transmission of *C. difficile* transmission from hands of healthcare workers are highly effective,[36] and data demonstrating the importance of the immune response and risk of developing CDI.[26]

Interestingly, epidemiological parameters linked to patient susceptibility, such as antimicrobial treatment rate, had little impact on *C. difficile* transmission (Figure 2). This appears contrary to CDI prevention recommendations and data indicating antimicrobial stewardship is effective at preventing CDI.[23,37] There are several potential explanations for this. In this study we did not differentiate between different classes of antibiotics and risk of CDI. This may have limited our ability to detect a reduction in CDI by limiting antibiotic exposures. A large percentage of patients were considered susceptible due to antimicrobial treatment, therefore the rate at which the resistant patients become susceptible patients was not a limiting factor in the *C. difficile* transmission. Conversely, most data to support antimicrobial stewardship to prevent CDI occur in outbreak settings in conjunction with other prevention efforts. It is possible antimicrobial stewardship by itself is less effective in non-outbreak situations or in the absence of efforts to reduce *C. difficile* transmission.

There are some limitations to this study. Actual *C. difficile* colonization prevalence on admission and at discharge from the study wards was not available. However colonization prevalence reported in the literature was used for the parameter estimates and subsequent assessment of colonization status conducted after the study period indicates the prevalence of *C. difficile* colonization on admission and discharge at the study hospital are consistent with the literature (5% and 15%, respectively, unpublished data). The diagnosis of CDI was based on the result of a toxin enzyme immunoassay in patients with diarrhea. Toxin enzyme immunoassays suffer from variable sensitivities, possibility missing true cases of CDI.[37] This often results in repeat testing and subsequently increases the risk of having a false positive result as well.[38] Transmission coefficients were identified as important parameters. Therefore, the different routes of transmission through contaminated health-care workers and environment will need to be considered explicitly in the model to design future interventions to prevent *C. difficile* transmission.

The epidemiology of *C. difficile* has changed dramatically in the last decade, with notable increases in CDI incidence and severity. Current prevention recommendations appear effective when combating CDI outbreaks, however they may be less effective at prevent endemic CDI.[39] Our study underscores the need to further evaluate the role of asymptomatically colonized patients in *C. difficile* transmission and identify methods to best prevent *C. difficile* transmission from these patients. The integration of *C. difficile* based transmission modeling with culture-based data available post-changes in CDI epidemiology, and the development of methods to rapidly and reliably identify asymptomatic *C. difficile* carriers, are necessary to have a complete understanding on which are the most cost-effective methods to prevent CDI, the most common healthcare-associated infection.

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APPENDIX

The deterministic differential equations for the model are as follows (parameters are defined in Table 2):

$$\frac{dR}{dt}=a_r\delta N+\theta S-k_rR-\alpha R \quad [1]$$

$$\frac{dS}{dt}=a_s\delta N+\alpha R+p\varepsilon D-\theta S-kS-\lambda S \quad [2]$$

$$\frac{dC^-}{dt}=a_{cn}\delta N+(1-f)\lambda S-\varphi C^--kC^- \quad [3]$$

$$\frac{dC^+}{dt}=a_{cp}\delta N+f\lambda S-kC^+ \quad [4]$$

$$\frac{dD}{dt}=a_d\delta N+\varphi C^--p\varepsilon D-k_dD \quad [5]$$

$$\lambda=\beta_c\left(C^-+C^+\right)+\beta_dD \quad [6]$$

$$N=R+S+C^-+C^++D \quad [7]$$

At the free disease equilibrium, the number of susceptible (S_0) can be described as a function of antibiotic prescription (α), colonization resistance restoration (θ), discharge rates (k, kr) and ward beds (N) as follows,

$$S_0=\frac{(a_sk_r+\alpha)N}{(\alpha+a_sk_r+(1-a_s)k+\theta)} \quad [8]$$

For the next generation matrix, we define the matrices F and V as

$$F=\left[\frac{\partial F_i(x)}{\partial x_j}\right]_{x=x_0} \text{ and } V=\left[\frac{\partial V_{i(x)}}{\partial x_j}\right]_{x=x_0}$$

where $F_i(x)$ is the number of new infections in the i^{th} compartment from x_j infectious individuals and $V_i(x)$ is the net change of individuals in the i^{th} compartment by any other means. The rates are evaluated at the disease free equilibrium $x=x_0$. For the model, F and V are given as follows:

$$F=\begin{bmatrix} (1-f)\beta_c S_0 & (1-f)\beta_c S_0 & (1-f)\beta_d S_0 \\ f\beta_c S_0 & f\beta_c S_0 & f\beta_d S_0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$V=\begin{bmatrix} k+\varphi & 0 & 0 \\ 0 & k & 0 \\ -\varphi & 0 & p\varepsilon+k_d \end{bmatrix}$$

$$V^{-1}=\begin{bmatrix} \frac{1}{k+\varphi} & 0 & 0 \\ 0 & \frac{1}{k} & 0 \\ \frac{\varphi}{(p\varepsilon+k_d)(\varphi+k)} & 0 & \frac{1}{p\varepsilon+k_d} \end{bmatrix}$$

The next generation matrix, K, is FV^{-1}. The entry (i,j) of K is the expected number of secondary infections in compartment i produced by individuals initially in compartment j.

$$K=FV^{-1}=\begin{bmatrix} K_{c^-c^-} & K_{c^-c^+} & K_{c^-d} \\ K_{c^+c^-} & K_{c^+c^+} & K_{c^+d} \\ 0 & 0 & 0 \end{bmatrix}$$

Where,

$$K_{c^-c^-}=\frac{(1-f)\beta_c S_0}{\varphi+k}+\frac{(1-f)\varphi\beta_d S_0}{(p\varepsilon+k_d)(\varphi+k)} \quad [9]$$

$$K_{c^-c^+}=\frac{(1-f)\beta_c S_0}{k} \quad [10]$$

$$K_{c^-d}=\frac{(1-f)\beta_d S_0}{p\varepsilon+k_d} \quad [11]$$

$$K_{c^+c^-}=\frac{f\beta_c S_0}{\varphi+k}+\frac{f\varphi\beta_d S_0}{(p\varepsilon+k_d)(\varphi+k)} \quad [12]$$

$$K_{c^+c^+}=\frac{f\beta_c S_0}{k} \quad [13]$$

$$K_{c^+d}=\frac{f\beta_d S_0}{p\varepsilon+k_d} \quad [14]$$

Each entry (i, j) of the K matrix represents the expected number of secondary colonizations in compartment i produced by individuals initially in compartment j. The basic reproduction number is the spectral radius of the matrix K,

$$R_0=\rho(K)=\frac{(1-f)\beta_c S_0}{\varphi+k}+\frac{(1-f)\varphi\beta_d S_0}{(p\varepsilon+k_d)(\varphi+k)}+\frac{f\beta_c S_0}{k} \quad [15]$$

Stochastic model

We developed an individual-based stochastic model based on Figure 1. A combined algorithm based on the Gillespie direct and first reaction methods was used to simulate our individual-based stochastic model[40]. In our simulations, when patients were admitted to hospital or moved to a different state, they were supposed to stay in a constant duration (depending which state they were in) prior to discharge unless they moved to another state. To utilize full beds in a ward, the admission was assumed to be immediate once a patient was discharged. Our model is a modified continuous time Markov chain model, where time is continuous, $t\in[0,\infty)$, and the state space is discrete. The state space for the model is,

$$\vec{X}(t)=(R(t),S(t),C^{-}(t),C^{+}(t),D(t))$$

and $\Delta\vec{X}(t)=\vec{X}(t+\Delta t)-\vec{X}(t)$. The probability of a transition is

$$P\left\{\Delta\vec{X}(t)=(r,s,c^{-},c^{+},d)\,|\vec{X}(t)\right\}$$

We assume that Δt is sufficiently small so that the values of r, s, c^{-}, c^{+}, d is nonzero. There are 11 possible changes in state where at least one of the r, s, c^{-}, c^{+}, d is nonzero. The transition probabilities for the possible changes between states and five types of discharge events are defined as follows,

Events	Transition probability	Changes
Restoration colonization resistance	$\theta S\Delta(t)+o(\Delta t)$	$r=1,s=-1$
Antibiotic treatment	$\alpha R\Delta(t)+o(\Delta t)$	$r=-1,s=1$
Treatment success	$p\varepsilon\Delta(t)+o(\Delta t)$	$s=1$, $d=-1$
Colonization without immune response	$(1-f)\lambda S\Delta t+o(\Delta t)$	$s=-1$, $c^{-}=1$
Colonization with immune response	$f\lambda S\Delta t+o(\Delta t)$	$s=-1$, $c^{+}=1$
Disease	$\varphi C^{-}\Delta(t)+o(\Delta t)$	$c^{-}=-1$, $d=1$
	Duration	
Discharge R	$1/k_r$	$r=-1$
Discharge S	$1/k$	$s=-1$
Discharge C^{-}	$1/k$	$c^{-}=-1$
Discharge C^{+}	$1/k$	$c^{+}=-1$
Discharge D	$1/k_d$	$d=-1$

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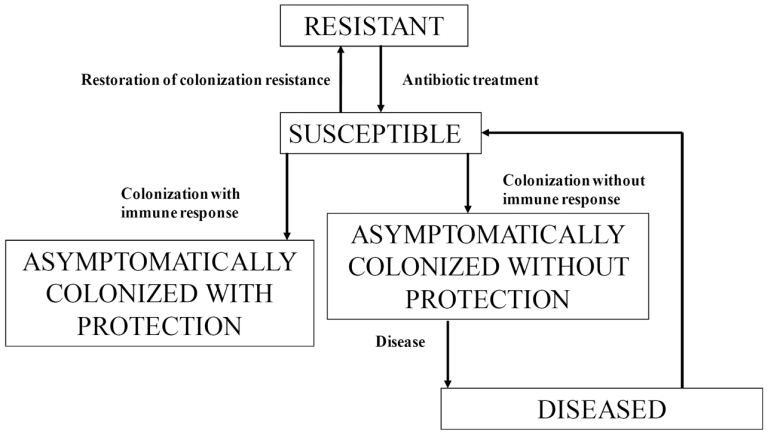

Figure 1.
Flow diagram of the epidemiological model for *Clostridium difficile* transmission in a hospital ward. Five transition states are included: resistant (R), susceptible (S), asymptomatically colonized without protection against *C. difficile* infection (C^-), asymptomatically colonized with protection against *C. difficile* infection (C^+), and diseased patients (D).

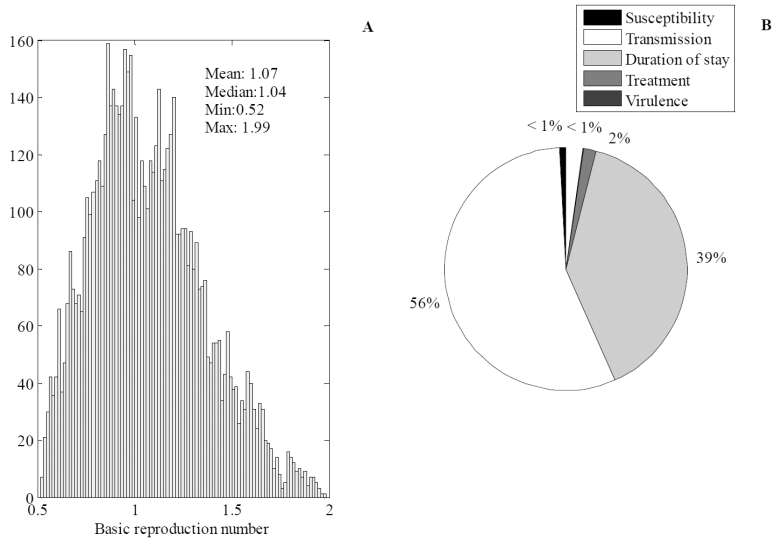

Figure 2.

Distribution of the basic reproduction number when parameters are varied (A) and contribution of the grouped parameters to the variation observed in the basic reproduction number (B). We grouped the parameters within the following groups: (1) parameters that determine patient susceptibility (a_s, α, θ, k_r), (2) transmission (β_c, β_d), (3) duration of stay of colonized individuals (k, k_d), (4) treatment (ε, p), and (5) virulence (f, φ). Parameters are defined in Table 2.

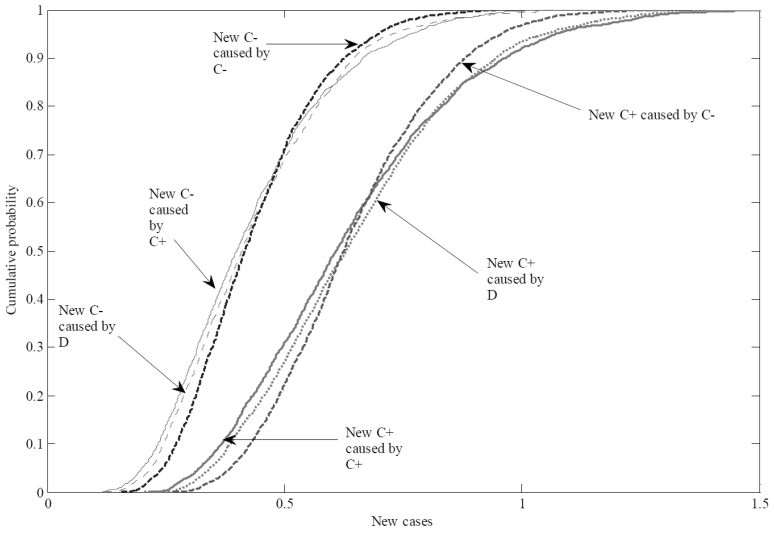

Figure 3.

Number of new secondary cases (C^- and C^+) of colonization generated by each type of admitted colonized patients (C^-, C^+, D).

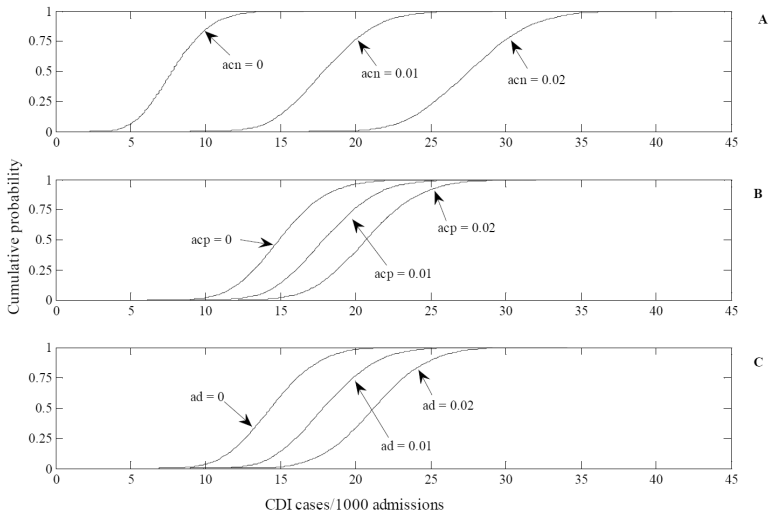

Figure 4.

Effect of varying the proportion of admitted colonized without immunity (a_{cn}) (A), colonized with immunity (a_{cp}) (B), and admitted diseased (a_d) (C) patients in the average *Clostridium difficile* infection (CDI) cases per 1000 admissions.

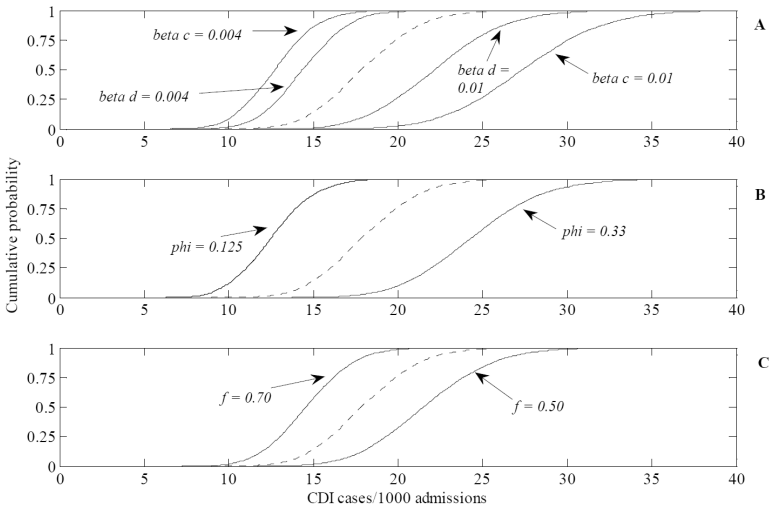

Figure 5.

Effect of varying the transmission coefficients (beta c and beta d) (A), the clinical disease rate (phi) (B), and the fraction of colonized patients that mount immune response (C) on *Clostridium difficile* infection cases per 1000 admissions. The dash line represents the simulation with the baseline parameter values.

Table 1

Summary of the transition states included in the epidemiological model for *Clostridium difficile* transmission based on four criteria: antimicrobial treatment, presence of the toxigenic *C. difficile*, immune response, and clinical symptoms.

	Antimicrobial treatment	**Presence of toxigenic *C. difficile***	**Immune response against *C. difficile***	***C. difficile* symptoms**
Resistant	−	−	−	−
Susceptible	+	−	−	−
Colonized without protection	+	+	−	−
Colonized with protection	+	+	+	−
Diseased	+	+	+/−	+

Table 2

List of parameters for the *Clostridium difficile* model.

Symbol	Description, units	Baseline value	Range used in the sensitivity analysis	Source
a_r	Proportion of admitted patients that are resistant, dmls[1]	0.75	--	Hosp. Data[2]
a_s	Proportion of admitted patients that are susceptible, dmls	0.22	0.15–0.29	Estimated[2]
a_{cr},a_{cp}	Proportion of admitted patients that are colonized, dmls	0.01	--	Estimated
a_d	Proportion of admitted patients that are diseased, dmls	0.01	--	Hosp. Data
α	Antibiotic prescription rate, 1/day	0.5	0.35–0.65	Hosp. Data
θ	Restoration rate of colonization resistance, 1/day	0.033	0.023–0.043	[22]
$\beta_c\beta_d$	Transmission coefficients, 1/(ind*day)	0.007	0.004–0.01	Estimated
f	Fraction of colonized patients that mount immune response, dmls	0.60	0.45–0.75	[26]
ε	Treatment rate, 1/day	0.10	0.07–0.13	[24]
p	Probability of successful treatment, dmls	0.80	0.56–1	[24]
φ	Clinical disease rate, 1/day	0.2	0.14–0.26	[9,25]
kr	Discharge rate for resistant patients, 1/day	0.33	0.23–0.43	Hosp. Data
k	Discharge rate for susceptible and colonized patients, 1/day	0.15	0.105–0.195	Hosp. Data
kd	Discharge rate for diseased patients, 1/day	0.068	0.048–0.088	Hosp. Data

[1] dmls: dimensionless,

[2] Parameters obtained directly from the hospital data,

[3] values set to match observed attack rate.